View metadata, citation and similar papers at
brought to you by CORE
provided by Elsevier - Publisher Connector

Journal of the American College of Cardiology
Vol. 50, No. 1, 2007
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00

CORRESPONDENCE

Letters to the Editor

Diastolic Dysfunction and Heart Failure

*Theodore J. Kolias, MD, FACC

*University of Michigan Cardiovascular Center
CVC Cardiovascular Medicine
1500 E. Medical Center Drive
SPC 5853
Ann Arbor, Michigan 48109
E-mail: tkolias@umich.edu

doi:10.1016/j.jacc.2007.04.025

I would like to congratulate Dr. Persson and colleagues for their recently published echocardiographic substudy of the CHARM (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity)-Preserved trial (1). Their results emphasize the importance of an objective evaluation of diastolic function in determining prognosis of patients with heart failure and preserved systolic function. Interestingly, one-third of the patients in their study had no objective evidence of diastolic dysfunction, despite being enrolled in a study where they were presumed to have experienced heart failure. Furthermore, this group also had the best prognosis. The most likely explanation is that either 1) they were misclassified and did not have heart failure or 2) their heart failure was on the basis of a different mechanism altogether (i.e., they had neither diastolic nor systolic dysfunction), and whatever the underlying cause for their heart failure, it appears to be relatively benign. These possibilities illustrate the need for being more specific in how we assess and characterize patients with heart failure, particularly those with diastolic dysfunction. I believe the time has come for us to consider abandoning the "black box" term of "heart failure with preserved systolic function," because this likely lumps together a number of different disease entities. Rather than trying to avoid classifying patients with diastolic dysfunction because of the current limitations in assessment, efforts would be better directed toward striving to improve the detailed assessment of diastolic function. The study by Persson et al. (1) is a first step toward that end. In the future, newer techniques such as tissue Doppler, strain-rate imaging, and speckle tracking may lead to better understanding of this disease process.

As the investigators pointed out, their study had a relatively small proportion of patients with mild diastolic dysfunction, and the prognosis of these patients was essentially the same as those with normal diastolic function. These findings are in contrast with a previously published study by Redfield et al. (2) One possible explanation is that Persson et al. (1) varied their ranges of normal E/A ratio by age group. Whereas the mean E/A ratio is known to decrease with advancing age, the rationale for considering this "normal" is unclear, as it is widely accepted that the decreasing E/A ratio with advancing age reflects impairment in left ventricular relaxation that occurs with aging. As such, just as we do not consider a mildly elevated systolic blood pressure as "normal" in an elderly individual just because the average systolic blood pressure of older subjects is higher, the decrease in E/A ratio seen in elderly patients should also not be considered "normal." It is likely that were a standard E/A ratio used for all age groups, then the proportion of patients with mild diastolic dysfunction would be higher. It would be interesting to see if this approach would lead to increased differentiation among the 4 groups in the survival analysis.

REFERENCES

1. Persson H, Lonn E, Edner M, et al., for the Investigators of the CHARM Echocardiographic Substudy—CHARMES. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy—CHARMES. J Am Coll Cardiol 2007;49:687–94.
2. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

Reply

We thank Dr. Kolias for his congratulatory letter to us for our echocardiographic substudy in CHARM (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity) Preserved—the CHARMES trial, recently published in *JACC* (1). His comments are appreciated, and we would agree with him that it is important to consider abandoning the "black box" term of "heart failure with preserved systolic function" and that efforts would be better directed toward striving to improve the detailed assessment of diastolic function. We have been able to reclassify the patients in CHARMES to respond to the relevant question posed by Dr. Kolias. In the revised analysis we have retrieved data for a conventional Doppler-echocardiographic evaluation of 181 of the 312 patients entered in the trial, thus not using the N-terminal part of the pro-B-type natriuretic peptide (NT-proBNP) to distinguish between normal and pseudonormal diastolic function. We have used a non–age-related classification of diastolic function following the current guideline from the Mayo Clinic (2). The present analysis is a secondary, post hoc analysis in a smaller subset; therefore, the results have to be interpreted with caution.

The results do show that the proportion of patients with normal diastolic function is similar to the previous results in CHARMES, with 1 out of 3 patients being normal (see Table 1). The proportion of patients with mild diastolic dysfunction is slightly higher, although the proportion with normal and mild diastolic dysfunction is not significantly different from the original CHARMES study (60% vs. 55%). We can still show a graded relationship between severity of diastolic dysfunction and outcome. The relative risk for moderate to severe diastolic versus mild diastolic dysfunction is approximately 2, both for the end point of cardiovascular death or readmission for heart failure (CV1) and for the combined end point of cardiovascular mortality, rehospitalization for heart failure, myocardial infarction, and stroke (CV2). The

Table 1 Diastolic Function Groups in CHARMES and Subset: Cardiovascular Events in CHARMES Subset by Diastolic Function Group

Diastolic Function	CHARMES (n = 293)	CHARMES Subset (n = 181)	CV1	CV2
Normal	33% (n = 98)	31% (n = 56)	0%	0%
Mild dysfunction	22% (n = 65)	29% (n = 53)	7% (n = 4)	11% (n = 6)
Moderate dysfunction	37% (n = 109)	31% (n = 55)	15% (n = 8)	22% (n = 12)
Severe dysfunction	7% (n = 21)	9% (n = 17)	12% (n = 2)	18% (n = 3)

See text for explanations of end points CV1 and CV2.

relative risk for moderate to severe diastolic dysfunction versus mild dysfunction and normal function is 3.8 for CV1 and 3.9 for CV2. Mild diastolic dysfunction in this subset carries a similar prognosis as in the full study (7% vs. 6%), whereas the normal group has a nonsignificantly better prognosis (0% vs. 4%).

Thus, using a non–age-adjusted Doppler-echocardiographic classification of diastolic function, we can conclude that normal diastolic function and mild diastolic dysfunction are seen in 60% of the patients, and the relationship is graded between severity of diastolic dysfunction and outcome, with a 4-fold risk increase for moderate to severe diastolic dysfunction compared to normal diastolic function and mild diastolic dysfunction and 2-fold when comparing moderate and severe to mild dysfunction. The recalculations do not suggest a different picture from the previous primary analysis.

***Hans Persson, MD, PhD**
Eva Lonn, MD, MSc
Robert S. McKelvie, MD, PhD
for the Investigators of the CHARM Echocardiographic Substudy—CHARMES

*Karolinska Institutet
Department of Clinical Sciences
Danderyd Hospital
Stockholm, SE-182 88
Sweden
E-mail: hans.persson@ds.se

doi:10.1016/j.jacc.2007.04.024

REFERENCES

1. Persson H, Lonn E, Edner M, et al., for the Investigators of the CHARM Echocardiographic Substudy—CHARMES. Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy—CHARMES. J Am Coll Cardiol 2007;49:687–94.
2. Redfield M, Jacobsen S, Burnett J, Mahoney D, Bailey K, Rodeheffer R. Burden of systolic and diastolic ventricular dysfunction in the community. JAMA 2003;289:194–202.

Patent Foramen Ovale and Stroke Risk: The Devil Is in the Detail

The risk of stroke due to a patent foramen ovale (PFO) is real. Case reports document venous thrombi slipping through a foramen ovale to the left atrium and causing a stroke (1). The absolute risk for ischemic strokes in the presence of a PFO is unknown. The report of Di Tullio et al. (2) in a recent issue of the *Journal* may not shed more light on this question, because some "minor" details could end up seriously biasing their results.

As the investigators point out in their discussion, the prevalence of a PFO in the general population is close to one-quarter (3). The prevalence of a PFO in the current study is 15%. The most likely reason for this low PFO prevalence is underdiagnosis of interatrial shunts by transthoracic echocardiography (4). Otherwise, the researchers have to argue for a lower PFO prevalence in citizens from northern Manhattan compared to other cities of the U.S. Missing 4 of 10 PFOs would lower the hazard ratio (HR) for stroke in the PFO group compared to the non-PFO group, because these nondiagnosed shunts may increase the risk for stroke in the latter group. The results of the Cox regression models as presented would underestimate the actual hazard. In addition to the problem of underdiagnosis, a question arises regarding the patients studied. The mean age of patients participating in this project was 68 to 69 years. The association of a PFO and stroke has been demonstrated for patients <55 years (5) and is probably weaker in the elderly with competing conventional cardiovascular risk factors as hypertension, diabetes, and dyslipidemia.

Last but not least, Di Tullio et al. (2) should provide not only the HR for a stroke in the setting of a PFO, but also the corresponding HRs for other cardiovascular risk factors they corrected for.

***Markus Schwerzmann, MD**
Bernhard Meier, MD, FACC, FESC

*Cardiology
University Hospital Inselspital
Bern CH-3010
Switzerland
E-mail: markus.schwerzmann@insel.ch

doi:10.1016/j.jacc.2007.04.023

REFERENCES

1. Sibbing D, Overbeck M, Schmidt R, Gaa J, Barthel P. Patent foramen ovale with a riding vermicular thrombus causing paradoxical and massive pulmonary embolism. Eur Heart J 2006;27:2724.
2. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. J Am Coll Cardiol 2007;49:797–802.
3. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17–20.
4. Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. J Am Coll Cardiol 2005;46:1768–76.
5. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148–52.